Synopsis

"Synthesis of Novel 1,2,3-Triazoles and Evaluation of Their Biological Activity"

Submitted to: S.R.T.M. University, Nanded.

For Ph.D. Registration in Subject, Chemistry

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Title: Synthesis of 1,2,3-Triazoles and Evaluation of Their Biological Activity

(i) Introduction and Scope:

Among nitrogen-containing heterocyclic compounds, triazoles are privileged structure motif and flourishing in growth of triazole products, in particular, since the early 2000's, can be largely attributed to the birth of click chemistry[1]. 1,2,3-triazole containing hybrids and conjugates as promising lead compounds for diverse biomedical research[2]. These lead compounds paying attention to the widespread dangerous diseases and determinations as anti-HIV[3], anticancer, antimicrobial, anti-tubercular, antiviral, antidiabetic, antimalarial, anti-leishmanial, and neuroprotective agents. In recent years there has been growing interest in developing bacterial, peptide deformylase (PDF) as novel antibiotics. PDF is an iron-containing metalloenzyme, which catalyses the removal of the N-formyl group from the terminal methionine residue of nascent proteins[4,5]. PDF is essential for both gram-positive and gram-negative bacteria, since deformylation is a necessary step to complete protein biosynthesis and maturation. Due to its wide distribution in bacteria and its absence in mammalian cells, PDF represents an attractive target for the discovery of broad-spectrum antibacterial drugs[6,7]. Many PDF inhibitors have been reported in recent years[8–10]. Most of compound shares common structure commonly Hydroxamic acid. BB-83698 (British Biotech) compound was reported in clinical trials study some years ago[11].

(ii) Origin of the research problem:

According to the WHO, total of 1.5 million people died from TB in 2020 (including 214 000 people with HIV). Worldwide, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19 (above HIV/AIDS).

A number of new potential antitubercular drug candidates with novel modes of action have entered clinical trials in recent years[12]. Compounds such as gatifloxacin, moxifloxacin and linezolid, the already known antibiotics are currently being evaluated for their anti-TB activity.

Till now, a combination of drugs is used to treat TB and so far, we are not able to develop a single drug which could be used alone for the treatment of TB. In addition, large numbers of TB patients are co-infected with HIV, rendering the treatment more difficult as well as complex and increase the risk of adverse effects.

Triazoles exhibited excellent in vitro and in vivo anti-TB activities whereas hydroxamic acids were for their in-vitro inhibitory activity on Escherichia coli and staphylococcus aures PDF enzyme, since hydroxamic acid moiety was previously shown to be critical for good inhibitory activity. This functionality needs to be conserved in all triazole derivatives.

Here we wish to synthesize and preliminary evaluation of a new series of PDF inhibitors which would have potential for the treatment of TB having 1-substituted triazole-4- hydroxamic acids

(iii) Interdisciplinary relevance:

Compounds produced in this work would be tested for biological activity. The compounds which will show good inhibitory activity, will subject for further study in development of lead compounds.

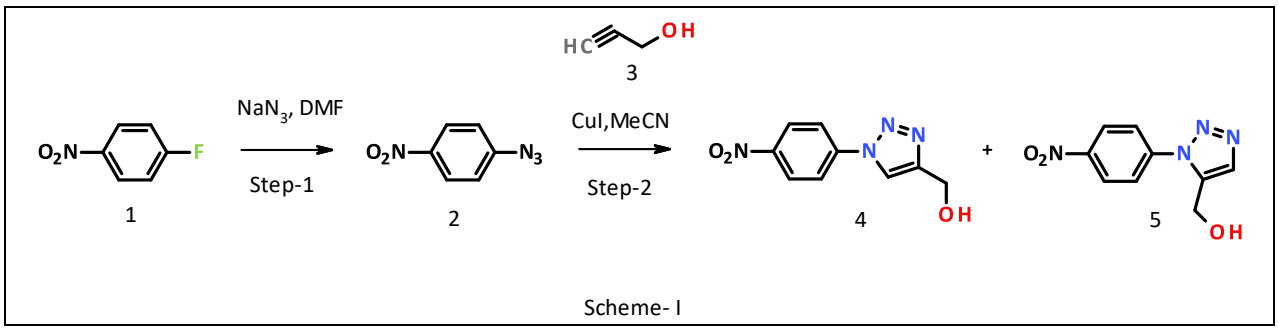
(iv) Review of Research and Development in the Subject:

a) International and National status:

This type compounds containing Triazole-4- hydroxamic acids have not been used at international levels by others for tuboroculo screening. Synthesis of various biological active molecules having hydroxamic acid moiety has been subject of many laboratories across the worldwide[13–15]. Triazole

derivatives are known for their diverse biological activity [16–22]. Reaction of 1-flouro-4-nitrobenzene with Sodium azide furnishes 1-azido- 4-nitrobenzene which on treated with propargyl alcohol, CuI in acetonitrile gives mixture of alcohols [23–25] **4** and **5** in (90:10). Significance of the study Triazole derivatives are known for their biological activity.

Reaction of 1-flouro - 4-nitrobenzene with Sodium azide furnishes 1-Azido- 4-nitrobenzene which on treated with propargyl alcohol, CuI in acetonitrile gives mixture of alcohols **4** and **5** in (90:10) **(Scheme-I)**.



Scheme- I

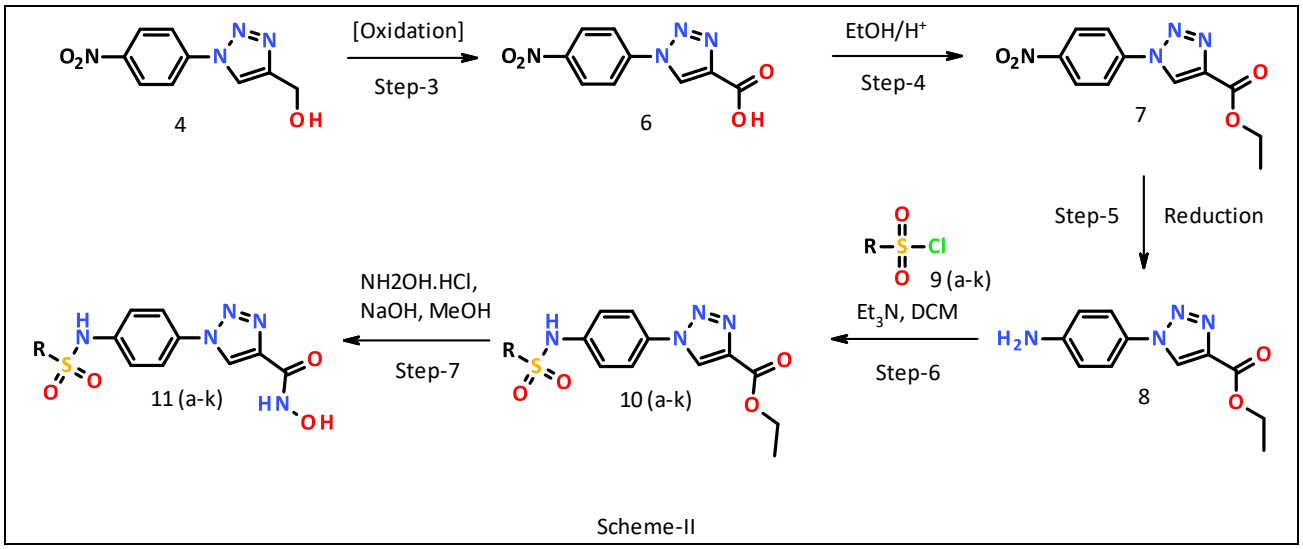
b) Objectives:

The alcohols **4** and **5** would prepare in large quantities and then will be used in the preparation of novel hydroxamic acid derivatives. The synthesized compounds will be subjected to investigate biological activity.

(v) Methodology:

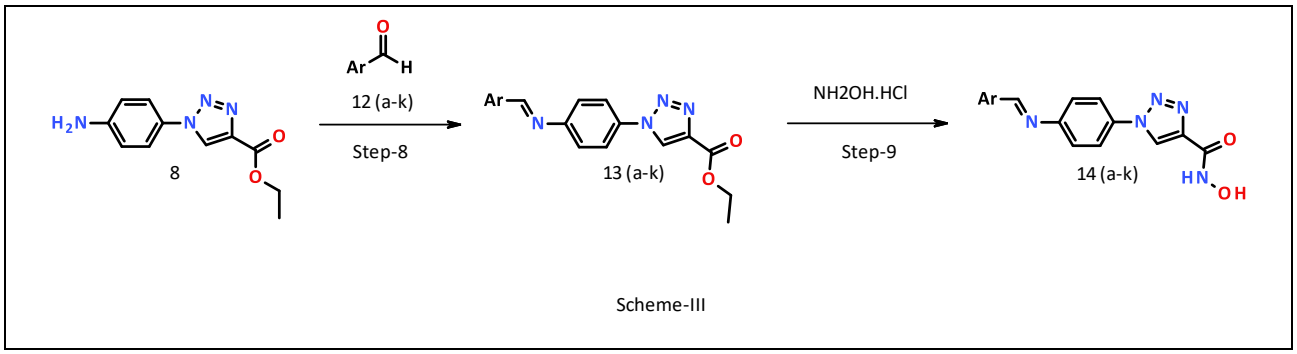
The first and foremost task is to separate the two regioisomer **4** and **5**. The alcohols are formed in 90:10 ratios and can be separated by column chromatography. After separation of these alcohols **4** and **5**, alcohol **4** was used for further reaction. It was oxidized using Jones reagent to its acid, which was further esterified using Ethanol and catalytic amount of H_2SO_4. Reduction of Nitro group gives amino compound **8**. Sulphonamide of compound **8** were prepared using different sulphonyl

chloride **10 (a-k)**. These sulphonamide derivatives then converted to Hydroxamic acids **11 (a-k) (Scheme-II)**.



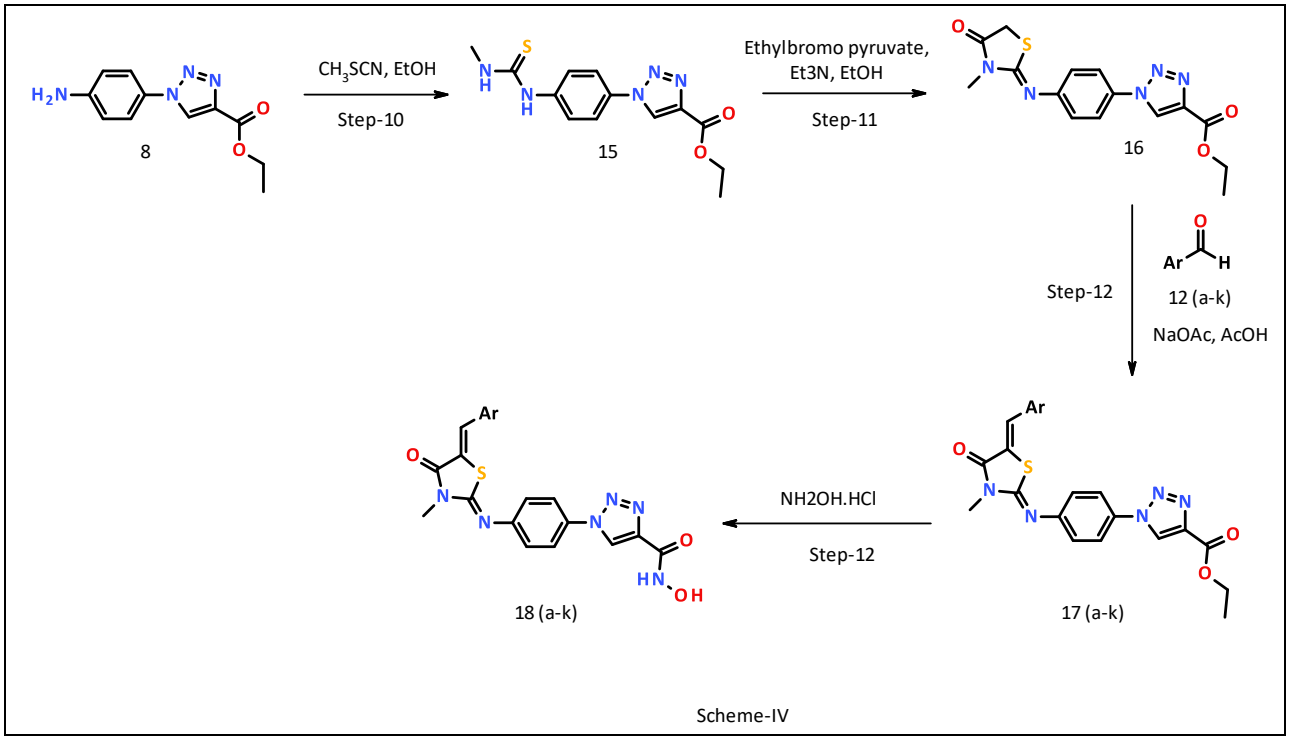
Scheme-II

Schiff's bases are also possessing biological activity[26], treatment of compound **8** with different aryl aldehydes in Ethanol using AcOH forms corresponding Schiff's bases **13 (a-k)**, which further transformed to Hydroxamic acids **14 (a-k) (Scheme-III)**.



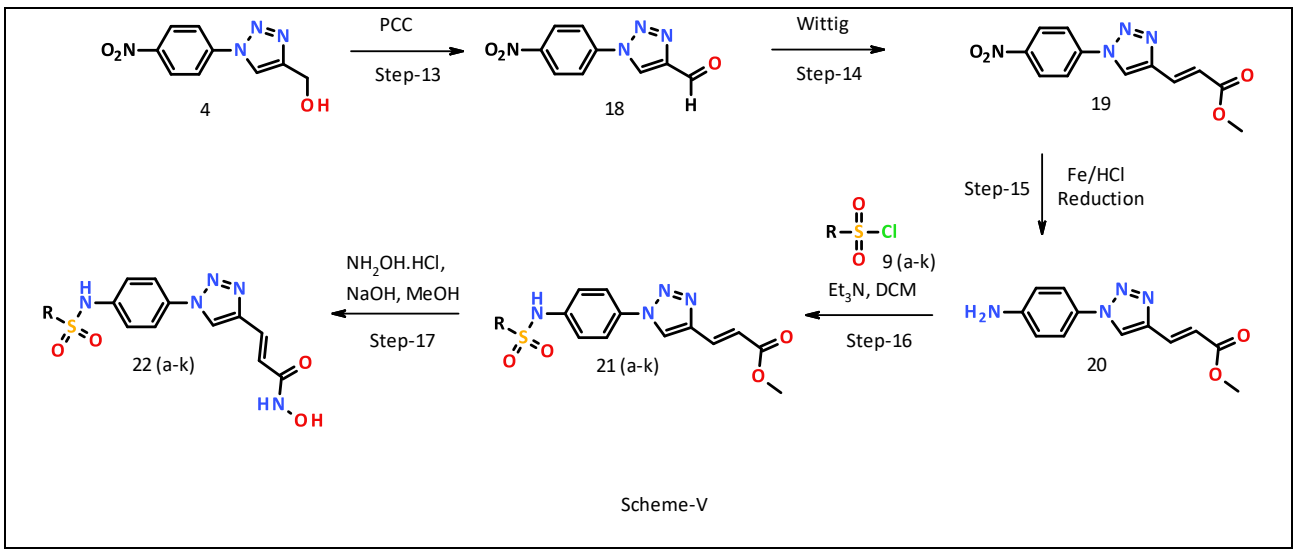
Scheme-III

4-thiazolidinones also possesses biological activity[27,28], thiazolidinone ring was constructed using methylisothiocynate and ethylbromoacetate and compound **8** to form iminothiazolidinone **16**, which on knovengel condensation with different aldehyde to compounds **17 (a-k)** and further they are converted to its respective hydroxamic acids **18 (a-k) (Scheme-IV)**



Scheme-IV

Cinnamoyl hydroxamic acids have strong biological activity[29,30]. Alcohol **4** on treatment with PCC forms triazole carboxaldehyde, using witting olefination compound **19** was prepared and then by using same methodology as Scheme-I, compounds **22 (a-k)** would furnish **(Scheme-V)**.

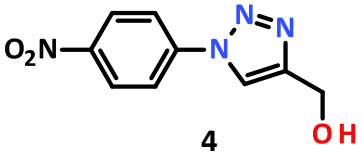


Scheme-V

(vi) Year wise work plan and targets to be achieve:

a) <u>First Year:</u>

i) In the first year we will establish investigate the synthesis of alcohols **4** and **5** (*Scheme- I*). These compounds will be confirmed by NMR, I.R. and Mass spectral data.



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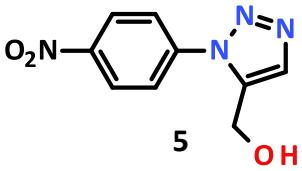

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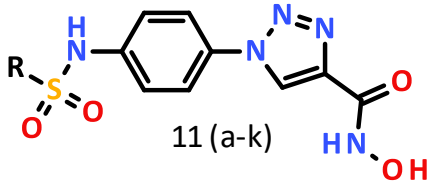
We will investigate the use of above alcohols **4** and **5** for the synthesis of sulphonamide derivative of Hydroxamic acids **11 (a-k)** (*Scheme-II*)

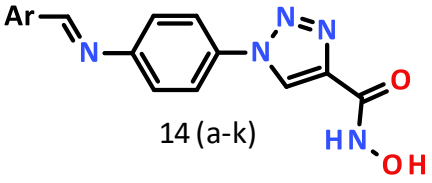


11 (a-k)

ii) Then these compounds will be subjected for biological activity.

b) <u>Second Year:</u>

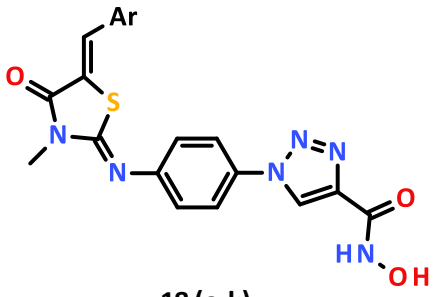
i) By using alcohols **4** and **5**, we will synthesize Schiff's base of hydroxamic acids **14 (a-k)** (*Scheme-III*)



14 (a-k)

ii) Then we will investigate the biological activity of these compounds

iii) We will use the alcohols **4** and **5** to synthesize the series of hydroxamic acid derivatives **18 (a-k)** (*Scheme-IV*) and characterize by using spectral techniques like 1H-NMR, Mass.

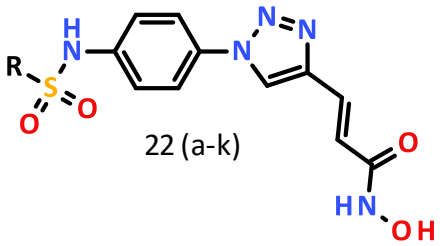


18 (a-k)

iv) These derivatives will be subjected to study biological activity.

c) <u>Third Year:</u>

i) The series of compounds **22 (a-k)** (*Scheme-V*) will be synthesized by using alcohols **4** and **5**.



22 (a-k)

ii) Then we will investigate the biological activity of these compounds

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Research Student **Research Guide**

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